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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/626,677	ISACSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 12-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5 and 12-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed August 28, 2003 has been entered. Claims 1, 12, 13, 14, 17-22 have been amended. Claims 23 and 24 have been newly added.

Accordingly, Claims 1, 4, 5, and 12-24 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Double Patenting

Applicant is advised that should claim 22 be found allowable, claim 24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the wording is identical.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1, 4, 5, and 12-22 stand rejected and Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-5 of the Office Action of Paper No. 4 (mailed 10/4/01), on pages 2-6 of the Office Action of Paper No. 9 (mailed 5/31/02), and on pages 3-6 of the

Office Action of Paper No. 14 (mailed 2/26/03), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a human patient suffering from Parkinson's disease by engrafting into said patient a population of recombinant cells. The recombinant cells are either recombinant embryonic stem cells or recombinant progenitor cells which are lineage-restricted to dopaminergic neurons. Although the preamble implies that the method will result in treatment of Parkinson's disease, no particular treatment effect is achieved.

At page 9 of the response, Applicants argue that the Zwaka reference does not suggest that electroporation of human ES cells is entirely unsuccessful. Applicants conclude that "for this reason alone, Zwaka proves that the instant specification enables the genetic modification of human ES cells. However, the instant specification does not provide any guidance regarding **electroporation** of human ES cells. On the contrary, the only guidance provided in the specification with regard to the transfection of human embryonic stem cells directs the skilled artisan to use **adenovirus**. Example 6 of the specification describes the transfections of human ES cells with an adenovirus carrying the β-galactosidase reporter gene. Alhough the disclosure states that "[s]taining for expression of the β-galactosidase marker gene was performed," no results are provided with regard to the detection of any β-galactosidase-expressing cells. Prior to the report of Eiges et al. (April 2001), human embryonic stem cells had never before been genetically modified. The reference demonstrates the use of the transfection protocol of ExGen 500 to transfect human ES cells, whereas the instant specification directs the skilled artisan to use **adenovirus** transduction for the genetic modification of human ES cells. To date, there are no reports of successful transduction of human ES cells using adenovirus. While the instant specification suggests using adenovirus for the transduction of human ES cells, the specification does not demonstrate success with adenovirus.

The experiments described in the specification further fail to permit the skilled artisan to obtain a cell composition derived from **human** ES cells that is suitable for transplantation into human patients. The specification does not provide sufficient guidance regarding which promoters are active in human ES cells or a teaching of which promoter should be used to drive expression of Nurr1 and/or PTX-3. As a prerequisite to cell transplantation, the skilled artisan must be able to produce the cell compositions that will be transplanted. Thus, the specification fails to teach the skilled artisan how to obtain **cell compositions** that are suitable for transplantation into humans. The art teaches that the directed differentiation of ES cells leads to a heterogeneous mixture of cells and the instant specification does not teach how to use a mixed population of cells for therapeutic transplantation. Mouse ES cells are not human ES cells. They exhibit widely varying characteristics compared to human ES cells and therefore have not been predictive of the behavior of human ES cells.

The behavior of mouse ES cells is not predictive of human ES cells. As discussed in the previous Office Action, mouse ES cells behave quite differently from human ES cells. Human ES cells have different characteristics and require the development of different protocols for their genetic modification, culture, and *in vitro* differentiation. Odorico et al. (2001) provides a discussion of multilineage differentiation from human embryonic stem cells and points out that many barriers remain in the way of successful clinical trials that employ the transplantation of human ES cells or ES cell-derived cells. The reference provides a detailed discussion of the differences between human ES cells and mouse ES cells. The reference points out that human and nonhuman primate ES cells share a similar morphology that is distinct from mouse ES cells. Furthermore, human ES cells grow more slowly than mouse ES cells. Human ES cells differ from murine ES cells with regard to cell-surface antigen phenotype. Human ES cells also differ from mouse ES cells in their *in vitro* culture requirements for undifferentiated growth. Mouse ES cells require leukemia inhibitory factor (LIF) for undifferentiated proliferation, whereas LIF alone is not sufficient to prevent differentiation of human ES cells *in vitro*. It

is important to note that, directed differentiation of ES cells results in mixed populations of cells. Odorico et al. points out that the heterogeneous nature of development in culture has hampered the use of ES cell derivatives in transplantation studies (page 198, column 2). The reference further emphasizes that achieving a therapeutic result will mandate integration of the transplanted cells into the host tissue in a functionally useful form (page 199, column 2). The reference acknowledges the complex structural integration required for transplantation into the neuronal circuitry (page 200, column 1, paragraph 1).

At pages 12-16 of the response, Applicants argue that the 6-OHDA lesion model is predictive of PD in human patients and that to dismiss it is to disregard over thirty years of characterization and correlation of the model with the human condition. However, the rejection is not based on the lack of correlation between the animal model and the human condition, but rather is based on the lack of correlation between mouse ES cells and human ES cells. The instant specification teaches that human ES cells should be used in humans and one of skill in the art would not attempt to use mouse ES cells in humans. Thus, specific teachings with regard to the manipulation and characterization of human ES cells is needed before therapeutic transplantation can become a reality.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of cell types that could be used, and the unpredictability for achieving a therapeutic effect upon the transplantation of human ES cells, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a human patient for therapeutic benefit.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

Written Description

Claims 19-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of treating a human patient suffering from Parkinson's disease by (i) providing recombinant progenitor cells which are lineage-restricted to dopaminergic neurons and (ii) engrafting into said patient said recombinant cells.

The specification does not provide a written description for the entire genus of "recombinant progenitor cells which are lineage-restricted to dopaminergic neurons." The specification does not describe the various types of recombinant progenitor cells (committed precursors) that could be used in the claimed method. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, not even a single species is described by its complete structure because the specification does not teach a promoter to use in **human** cells for driving expression of the nucleic acid encoding Nurr1 or the nucleic acid encoding PTX-3. The specification does not indicate at what point the recombinant cells become committed progenitor cells and the claims do not require expression of the Nurr1- or PTX-3-encoding nucleic acids. In the absence of expression of a nucleic acid such as the two described in the specification, other factors would be required to induce the cells to become lineage-restricted to dopaminergic neurons, but the specification does not describe other factors that could be used to induce such a phenotype. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, no species beyond those cells expressing either Nurr1 or PTX-3 have been described by other relevant identifying characteristics. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the entire genus of recombinant progenitor cells that could be used in the claimed method. Thus, it is concluded that the written description requirement is not met for the genus of progenitor cells recited in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, and 12-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 5, and 12-22 remain indefinite and newly added Claims 23 and 24 are indefinite in their recitation of "a method of treating a human patient suffering from Parkinson's disease" because the preamble implies that a treatment effect will be achieved, but in fact no particular treatment effect is achieved. Thus, the preamble is in conflict with the body of the claim.

At page 16, paragraph 4 of the response, Applicants argue that there is nothing indefinite about "treating a human patient" because a person of ordinary skill in the art immediately recognizes that a medical treatment may be administered to effect a variety of outcomes, including cure and relief of symptoms.

In response to applicant's arguments, the recitation "treating a human patient suffering from Parkinson's disease" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, the process steps are able to stand alone. In Claim 1, for example, the process steps result in the engraftment of recombinant cells in the patient.

Claims 19-24 are indefinite in their recitation of "recombinant progenitor cells which are lineage-restricted to dopaminergic neurons" and "wherein said recombinant cells are embryonic stem cells" because embryonic stem cells are **not** lineage-restricted. Thus, the claim language is contradictory.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 19 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,284,539 (Bowen et al.; filed 10/9/98).

Claim 19 is directed to a method of treating a human patient suffering from Parkinson's disease by engrafting into said patient a population of recombinant progenitor cells which are lineage-restricted to dopaminergic neurons. Although the preamble implies that the method will result in treatment of Parkinson's disease, no particular treatment effect is achieved or required.

Bowen et al. disclose that introducing the gene encoding Nurr1 into central nervous system (CNS) stem cells causes them to adopt a dopaminergic fate. The reference further discloses that the cells can be used for transplantation into patients suffering from Parkinson's disease.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER